in Appendices A and B submitted herewith. Appendix A is a marked-up copy of the amended claim and Appendix B is a clean copy of the amended claim.

REMARKS

Claims 1-9, 11, and 14-15 are presently pending in the captioned application. The amendments are presented in the expectation that the amendments will place this application in condition for allowance. The amendments were made to further emphasize that the presently claimed compositions are orally efficacious. The amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of claims 1-12, 14, and 15 under 35 U.S.C. § 103

The Office Action states that claims 1-12, 14, and 15 are rejected under 35 U.S.C. § 103 as being obvious. The Office Action rejects claims 1, 2, 5-12, and 14 over Nath et al. (Novel Met-Enkephalin Analogue, Pharm. Res. Vol. 31, No. 5, pages 269-273 (1995)) in view of Chiesi et al. (U.S. Patent No. 5,855,916); claims 1-3 and 7-11 over European Patent Application No. 0 463 653 ("'653") in view of Nath et al.; claims 1, 2, 4, 7-12, and 14 over Hora et al. (U.S. Patent No. 5,977,856) in view of Nath et al.; and claims 1, 7-12, and 15 over French Patent 2 710 268 ("'268") in view of Nath et al.

Applicants respectfully traverse this rejection because all three prongs for a *prima facie* case of obviousness have not been established for each of the rejections. Specifically, all the claim limitations are not present in the cited references and one of ordinary skill in the art would have no motivation to modify the cited references into the present invention.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) that some suggestion or motivation to modify the references exists; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all the claim limitations. In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

1. Rejection of claims 1, 2, 5-12 and 14 over Nath et al. in view of Chiesi et al.

As a basis for the rejection the Office Action states:

> Claims 1, 2, 5-12, and 14 are rejected under 103 U.S.C. 103(a) as being obvious over the Nath et al article in view of Chiesi et al. The Nath et al article teaches the

highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. The Nath et al article does not teach the opioid peptide in combination with a cyclodextrin derivative. Chiesi et al teach forming an inclusion complex of a basic drug and a cyclodextrin such as hydroxypropyl-β-cyclodextrin and dimethyl-β-cyclodextrin. The inclusion complex results in improved storage stability and enhanced water solubility and bioavailabilty for the drug. The drug is to be administered orally or parenterally. See, e.g. column 3, lines 15-21; column 8, lines 54-56; and claim 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al in order to form inclusion complexes for pharmaceutical administration because the opioid peptide of the Nath et al article is a basic drug as required by Chiesi et al and because combining the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al would have been expected to increase the solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and cyclodextrin derivative in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicant's arguments filed May 3, 2002 have been fully considered but they are not persuasive.

Applicants contend that the compound of the Nath et al article does not include the N-methylphenylalanyl group required by Applicants' claims. The examiner disagrees. the "MePhe" group of the Nath et al article is synonymous with the "-methylphenylalanyl" group required by Applicants' claims, both signifying that the amino group of a phenylalanine residue is substituted with a methyl group. The compound of the Nath et al article and the opioid peptide recited in Applicants' claims are the same compound.

Applicants contend that the "consisting essentially of" language present in the claims excludes the acid of Chiesi et al...However, "consisting essentially of" language excludes from Applicants' claims only those components which would materially affect the basic and

novel characteristics of Applicants' claimed composition, with the burden being upon Applicants to make such a showing. See In re De Lajarte, 143 USPQ 256 (CCPA 1956) and MPEP 2111.03. Applicants have not submitted any evidence which would satisfy this burden.

Applicants contend that there is no motivation to combine the compound of the Nath et al article with the cyclodextrins of the other references because a person of ordinary skill in the art would recognize that the compound of the Nath et al article is already soluble in water and stable and therefore does not require improved water solubility or stability. However, Applicants have not provided any explanation as to why a person of ordinary skill in the art would recognize that the compound of the Nath et al article is already soluble in water and stable. Further, unless a drug is perfectly water soluble and perfectly stable (and the examiner is not aware of any drug which matches either of these criteria), then there is always motivation in the art to improve water solubility and/or stability. Finally, Chiesi et al provide the additional motivation of improved bioavailability...Any of these motivations is sufficient to support prima facie obviousness. Again, the motivation to establish prima facie obviousness need not be the same as Applicants'.

Applicants cite to the Uekema et al article as establishing that there is no reasonable expectation of success in forming orally available inclusion complexes containing the specific peptide of the invention. However, Applicants have not provided and made of record a copy of this article, and the article is not available in the Scientific and Technical Information Center, and accordingly the examiner can not rely upon this article to establish that there is no reasonable expectation of success. The examiner does note, however, that the date of the article as reported in Applicants' Remarks is 1994, and that whether or not there is a reasonable expectation of success must be established at the time Applicants' invention was made, i.e. in 2000. Because Chiesi et al...were published after Uekema et al article and before Applicants' filing date, it is unlikely that the Uekema et al article can be relied upon to demonstrate that later developments in the art do not create a reasonable expectation of success in combining opioid peptides with cyclodextrins.

Applicants argue that a peptide:cyclodextrin ratio of 1:2 is more effective for oral delivery than a 1:1 ratio, whereas the reverse is true for transdermal delivery.

However, Applicants have not provided evidence of this in appropriate form under 37 CFR 1.132, which is necessary in order to rely upon unexpected results to rebut a prima facie case of obviousness. Further, the rejected claims are not limited to peptide:cyclodextrin ratios of 1:2, and therefore the unexpected results discussed in Applicants' remarks are not commensurate in scope with Applicants' claims.

Express teachings are never necessary to support prima facie obviousness. See MPEP 2144, first full paragraph, first sentence. Further, Chiesi et al...already establish a reasonable expectation of success that various drugs can be usefully combined with cyclodextrins, and therefore combination of the particular drug of the Nath et al article with cyclodextrins would reasonably have been expected to be successful for the purposes expressed in Chiesi et al...Applicants have not indicated what parameters and possibilities would have to be tried until a successful combination was arrived at. The one parameter recited in Applicants' claims, i.e. opioid peptide:cyclodextrin molar ratio, is routinely determined and optimized by one skilled in the art. To date, Applicants have not supplied evidence that there are any critical parameters necessary to successfully combine an opiod peptide and a cyclodextrin. Unexpected results must be demonstrated, not alleged.

Applicants contend that their invention satisfies a long-felt need in the art. However, a long-felt need in the art must be demonstrated under 37 CFR 1.132. See MPEP 716.04 for the type of evidence needed to establish such secondary considerations of non-obviousness.

Again, the Examiner emphasizes that the motivation to combine prior art references need not be the same as Applicants. See MPEP 2144 under "Rationale Different From Applicants' Is Permissible". Further, while Applicants' arguments stress that the claimed compositions have improved oral efficacy, Applicants' claims clearly contemplate non-oral administration of the compositions (see, e.g., the reference to injections in claim 10, and the reference to transdermal or rectal administration in claim 12). It is irrelevant that the prior art references do not teach or suggest oral administration where Applicants' claims do not require oral administration. Applicants have not provided any evidence that the compounds disclosed by Chiesi et al...are not orally efficacious. Note that the issue of whether or not prior art compositions are orally

efficacious is different than the issue of whether or not prior art compositions are disclosed to be orally efficacious.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

The presently claimed invention relates to novel inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the sole essential components. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

Chiesi et al. do not remedy these deficiencies. Chiesi et al. disclose multicomponent inclusion complexes containing a basic-type drug, a cyclodextrin, and an acid as the essential components. Chiesi et al. teach that the acid is the critical component to establishing the water solubility of the inclusion complexes. In fact, Chiesi et al. specifically disclose that "the present invention relates to the use of an acid in the preparation of

complexes with a cyclodextrin...with the purpose of increasing the water solubility of the cyclodextrin itself." (See column 2, lines 8-12). Chiesi et al. provide no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the basic-type drugs used in the disclosed inclusion complexes. Additionally, Chiesi et al. provide no teaching for inclusion complexes that do not contain an acid as an essential component.

Applicants claims as presently amended are limited to inclusion complexes containing an opioid peptide and a cyclodextrin derivative as the only essential components. Neither reference cited by the Examiner teaches inclusion complexes having only these two essential components. As shown above, Nath et al. merely teaches a particular compound by itself, without inclusion of a cyclodextrin derivative. Likewise, Chiesi et al. teach inclusion complexes which require a basic-type drug, a cyclodextrin derivative, and an acid. The acid is a critical component of the inclusion complexes taught by Chiesi et al. since Chiesi et al. disclose that the acid itself provides the desired increase in water solubility. In contrast, the presently claimed inclusion complexes do not contain an acid to increase water solubility.

The transition phrase "consisting essentially of" is commonly used to signal a partially open claim in a patent. PPG Industries Inc. v. Guardian Industries Corp., 48 USPQ2d 1351, 1353 (Fed. Cir.

1998). Use of this transitional phrase in a claim indicates the claim necessarily includes the listed ingredients and "is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." Id. at 1353-54. An unlisted ingredient has a material effect on the characteristics of the invention if the effect is of importance or of consequence to those of ordinary skill in the relevant art. Id. at 1354. "Consisting essentially of" excludes the addition of another ingredient which materially affects the characteristics of the invention, either positively or negatively. Water Technologies Corp. v. Calco Ltd., 7 USPQ2d 1097, 1102 (Fed. Cir. 1988); Reese v. Hurst, 211 USPQ 936, 943 (C.C.P.A. 1981); In re Garnero, 162 USPQ 221, 223 (C.C.P.A. 1969).

The Examiner has submitted it is necessary for applicants to submit evidence showing that the "consisting essentially of" language in the present claims excludes the acid component shown be Chiesi et al. as a component which materially affects the basic and novel characteristics of the claimed composition. This is unnecessary in the present case, however, as the Chiesi et al. reference on its face demonstrates that the acid component materially effects the characteristics of the claimed invention, i.e. the water solubility of the inclusion complexes.

In particular, the Examiner has admitted on the record that water solubility is a basic property of the claimed invention,

stating the alleged combination "would have been expected to increase the solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents." Further, the Chiesi et al. reference explicitly sates "the present invention relates to the use of an acid...with the purpose of increasing the water solubility of the cyclodextrin itself." Clearly, this effect would be "of importance or of consequence to those of ordinary skill in the relevant art." Accordingly, the Chiesi et al. reference on its face demonstrates that the acid component materially effects the water solubility of the inclusion complexes, i.e. a characteristic of the claimed invention. It does not matter whether this is a positive or a negative effect; all that is necessary to avoid inclusion of this unrecited element in a claim reciting the "consisting essentially of" transition phrase is that the element have some effect on a basic characteristic of the invention.

Additionally, a person of ordinary skill in the art would recognize that the opioid peptide used according to the presently claimed invention is already soluble in water and stable. Accordingly, this peptide does not require improved water solubility or stability. The presently claimed invention, then, is patentably distinct from the references cited by the Examiner. A person of ordinary skill in the art would have had no reasonable expectation of success in forming orally available inclusion

complexes containing only the presently claimed specific peptide as well as a cyclodextrin, without an additional acid, as required by Amgen, Inc. v. Chugai Pharm. Co..

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of Chiesi et al. and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 2, 5-9, 11, and 14.

2. Rejection of claims 1-3 and 7-11 over EP '653 in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1-3 and 7-11 are rejected under 103 U.S.C. 103(a) as being obvious over the European Patent Application '653 in view of the Nath et al article. The European Patent Application '653 teaches combining drugs, including peptide drugs such as enkephalins, with cyclodextrins, especially B-cyclodextrin. The combination permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs. See, e.g., column 1, lines 8-24; column 4, lines 4-11; and column 5, lines 31-36. The European Patent Application '653 does not teach administration of Applicant's particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the European Patent Application '653 because the opioid peptide of the Nath et al article is a specific known example of the peptide and enkephalin drugs which are contemplated by the European Patent Application '653 and because administering the opioid peptide of Nath et

al nasally in the pharmaceutical formulations of the European Patent Application '653 would avoid problems of poor absorption after oral administration and of undesirable metabolism as taught by the European Patent Application '653. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicant's arguments filed May 3, 2002 have been fully considered but they are not persuasive.

Applicants contend that the compound of the Nath et al article does not include the N-methylphenylalanyl group required by Applicants' claims. The examiner disagrees. the "MePhe" group of the Nath et al article is synonymous with the "-methylphenylalanyl" group required by Applicants' claims, both signifying that the amino group of a phenylalanine residue is substituted with a methyl group. The compound of the Nath et al article and the opioid peptide recited in Applicants' claims are the same compound.

Applicants contend that the "consisting essentially of" language present in the claims excludes...the enhancer of absorption at a mucosal surface of the European Patent Application '653. However, "consisting essentially of" language excludes from Applicants' claims only those components which would materially affect the basic and novel characteristics of Applicants' claimed composition, with the burden being upon Applicants to make such a showing. See In re De Lajarte, 143 USPQ 256 (CCPA 1956) and MPEP 2111.03. Applicants have not submitted any evidence which would satisfy this burden.

Applicants contend that there is no motivation to combine the compound of the Nath et al article with the cyclodextrins of the other references because a person of ordinary skill in the art would recognize that the compound of the Nath et al article is already soluble in water and stable and therefore does not require improved water solubility or stability. However, Applicants have not provided any explanation as to why a person of ordinary skill in the art would recognize that the compound of the Nath et al article is already soluble in water and stable. Further, unless a drug is perfectly

water soluble and perfectly stable (and the examiner is not aware of any drug which matches either of these criteria), then there is always motivation in the art to improve water solubility and/or stability. Finally,...the European Patent Application provides the additional motivation of nasal administration...Any of these motivations is sufficient to support prima facie obviousness. Again, the motivation to establish prima facie obviousness need not be the same as Applicants'.
Applicants cite to the Uekema et al article as establishing that there is no reasonable expectation of success in forming orally available inclusion complexes containing the specific peptide of the invention. However, Applicants have not provided and made of record a copy of this article, and the article is not available in the Scientific and Technical Information Center, and accordingly the examiner can not rely upon this article to establish that there is no reasonable expectation of success. The examiner does note, however, that the date of the article as reported in Applicants' Remarks is 1994, and that whether or not there is a reasonable expectation of success must be established at the time Applicants' invention was made, i.e. in 2000.
Applicants argue that a peptide:cyclodextrin ratio of 1:2 is more effective for oral delivery than a 1:1 ratio, whereas the reverse is true for transdermal delivery. However, Applicants have not provided evidence of this in appropriate form under 37 CFR 1.132, which is necessary in order to rely upon unexpected results to rebut a prima facie case of obviousness. Further, the rejected claims are not limited to peptide:cyclodextrin ratios of 1:2, and therefore the unexpected results discussed in Applicants' remarks are not commensurate in scope with Applicants' claims.
Express teachings are never necessary to support prima facie obviousness. See MPEP 2144, first full paragraph, first sentence. Further,...the European Patent Application '653...already establish a reasonable expectation of success that various drugs can be usefully combined with cyclodextrins, and therefore combination of the particular drug of the Nath et al article with cyclodextrins would reasonably have been expected to be successful for the purposes expressed in...the European Patent Application '653...Applicants have not indicated what parameters and possibilities would have to be tried until a successful combination was arrived at. The one

> parameter recited in Applicants' claims, i.e. opioid peptide:cyclodextrin molar ratio, is routinely determined and optimized by one skilled in the art. To date, Applicants have not supplied evidence that there are any critical parameters necessary to successfully combine an opiod peptide and a cyclodextrin. Unexpected results must be demonstrated, not alleged.
> Applicants contend that their invention satisfies a long-felt need in the art. However, a long-felt need in the art must be demonstrated under 37 CFR 1.132. See MPEP 716.04 for the type of evidence needed to establish such secondary considerations of non-obviousness.
> Again, the Examiner emphasizes that the motivation to combine prior art references need not be the same as Applicants. See MPEP 2144 under "Rationale Different From Applicants' Is Permissible". Further, while Applicants' arguments stress that the claimed compositions have improved oral efficacy, Applicants' claims clearly contemplate non-oral administration of the compositions (see, e.g., the reference to injections in claim 10, and the reference to transdermal or rectal administration in claim 12). It is irrelevant that the prior art references do not teach or suggest oral administration where Applicants' claims do not require oral administration. Applicants have not provided any evidence that the compounds disclosed by...the European Patent Application '653...are not orally efficacious. Note that the issue of whether or not prior art compositions are orally efficacious is different than the issue of whether or not prior art compositions are disclosed to be orally efficacious.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to inclusion complexes comprising an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a

cyclodextrin derivative. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

EP '653 does not remedy these deficiencies. EP '653 teaches combining drugs including peptide drugs such as enkephalins with an enhancer of absorption at a mucosal surface and a cyclodextrin. The reference further teaches that undesirable side-effects due to using an absorption enhancer alone may be avoided when an absorption enhancer is used in combination with a cyclodextrin. See Column 3, lines 9-15. The medicaments disclosed by EP '653 are useful for therapy via in intranasal route. In fact, EP '653 teaches that intranasal administration is used as an alternative to oral administration since the included "drugs are only absorbed poorly by an oral route or are extensively metabolised in the gastrointestinal tract or subjected to first pass metabolism in the liver." See column 1, lines 8-19. Additionally, EP '653 provides no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among

the drugs used in the disclosed medicaments. Further, the absorption enhancers are necessary to increase the permeability of the nasal mucosa in order to enable the disclosed intranasal administration. See column 1, lines 52-58.

In contrast, the presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy which are delivered orally rather than intranasally. Applicants appreciate the Examiner's suggestions in this regard and have accordingly amended the claims to emphasize that the present invention is directed to compositions which are orally efficacious, not compositions delivered e.g. intranasally.

The Examiner has submitted it is necessary for applicants to submit evidence showing that the compositions disclosed by EP '653 are not orally efficacious. This is unnecessary in the present case, however, as the EP '653 reference on its face demonstrates that the disclosed compositions are not orally efficacious.

In particular, EP '653 specifically discloses that the drugs used in the embodied medicaments "are only absorbed poorly by an oral route". This reference on its face, then, shows that the disclosed compositions are not orally efficacious; a person of ordinary skill in the art would not expect the disclosed compositions to be effective upon oral administration. In fact,

the EP '653 reference specifically relates to compositions delivered intranasally because they are not effective when administered orally.

In contrast, the opioid peptides included in the presently claimed inclusion complexes are effective by oral administration, a significant improvement over the teachings of the EP '653 reference. In fact, the data in Tables 2 and 3 of the instant specification, at pages 14 and 15, demonstrate that the presently claimed inclusion complexes are effective via oral administration. A person of ordinary skill in the art would have had no motivation to combine the references cited by the Examiner to arrive at the presently claimed invention as required by In re Fine in view of the fact that EP '653 teaches away from the presently claimed invention requiring a composition which is orally efficacious.

Further, applicants claims as presently amended are limited to inclusion complexes containing an opioid peptide and a cyclodextrin derivative as the only essential components. Neither reference cited by the Examiner teaches inclusion complexes having only these two essential components. As shown above, Nath et al. merely teaches a particular compound by itself, without inclusion of a cyclodextrin derivative. Likewise, EP '653 teaches inclusion complexes which require a peptide drug, a cyclodextrin derivative,

and an enhancer of absorption at a mucosal surface. The absorption enhancer is a critical component of the inclusion complexes taught by EP '653 since they are necessary for the enablement of the intranasal administration. In contrast, the presently claimed inclusion complexes do not contain an absorption enhancer.

The Examiner has submitted it is necessary for applicants to submit evidence showing that the "consisting essentially of" language in the present claims excludes the absorption enhancers shown by EP '653 as a component which materially affects the basic and novel characteristics of the claimed composition. This is unnecessary in the present case, however, as the EP '653 reference on its face demonstrates that the absorption enhancers materially effect the characteristics of the claimed invention, i.e. by enabling them to be used for intranasal administration.

Clearly, the mode of administration is a critical and novel feature of the presently claimed invention, as discussed above. Accordingly, the use of an absorption enhancer as disclosed by EP '653 to make the compositions effective for intranasal administration is "of importance or of consequence to those of ordinary skill in the relevant art" and affects the basic and novel characteristics of the presently claimed invention. The presently claimed invention, then, is patentably distinct from the references

cited by the Examiner.

Further, applicants note that although EP '653 states that any active drug substance may be used in the disclosed compositions, only drugs such as proteins and peptides such as insulin, gentamicin, glucagon, growth hormone, calcitonins and synthetic modifications thereof, enkephalins, interferons, etc. are specifically exemplified. However, EP '653 specifically discloses neither the presently claimed specific opioid peptide itself nor any other synthetic modification of enkephalin molecules. Further, EP '653 does not actually provide any practical demonstrations, in the form of Examples or otherwise, regarding the disclosed drugs. Accordingly, this reference is non-enabling for the combination asserted by the Examiner. In re Wiggins, 179 USPQ 421, 425 (C.C.P.A. 1973).

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of EP '653 and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1-3, 7-9, and 11.

3. Rejection of claims 1, 2, 4, 7-12, and 14 are rejected over Hora et al. in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1, 2, 4, 7-12, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over Hora et al in view of the

> Nath et al article. Hora et al teach combining polypeptide drugs with cyclodextrins, B-cyclodextrin, including hydroxyethyl-B-cyclodextrin. The combination improves the solubility and the stability of polypeptide drugs, and permits oral administration as well. . . . Hora et al do not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of Hora et al because the opioid peptide of the Nath et al article is a specific known example of the polypeptide drugs which are contemplated by Hora et al and because administering the opioid peptide of Nath et al in the pharmaceutical formulations of Hora et al. would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above- outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to inclusion complexes comprising an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

Hora et al. do not remedy these deficiencies. Hora et al. disclose a method and compositions for stabilizing and/or solubilizing polypeptide drugs be means of a cyclodextrin to obtain improved solubility and stability of the polypeptide drugs. This is achieved by combining the polypeptide with an effective solubilizing and/or stabilizing amount of a cyclodextrin, i.e. placing the polypeptide in an aqueous solution of the cyclodextrin. Accordingly, the polypeptide merely exists within the cyclodextrin aqueous solution; no reaction occurs between the cyclodextrin and the polypeptide-each exists as a separate component. Further, Hora et al. provide no teaching that opioid peptides, such as the specific opioid peptide according to the presently claimed invention, are included among the polypeptide drugs used in the disclosed combinations.

In contrast, the presently claimed invention relates to inclusion complexes consisting essentially of a specific opioid

peptide combined with a cyclodextrin derivative. Since the invention relates to inclusion complexes, it is inherent that the two components making up the complexes must react in some way to from the complexes. Accordingly, the resultant complexes represent an entirely new chemical entity as compared to the initial two components, sometimes even having a slight modification in the structure of these components in order to permit the inclusion complexes to be formed. Such complexes are neither disclosed nor even contemplated by the Hora et al. reference, which merely shows placing a polypeptide in an aqueous cyclodextrin solution. This procedure of Hora et al. will not result in any reactions, and accordingly will not result in the inclusion complexes that are presently claimed.

Further, applicants have observed that the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide combined with beta-cyclodextrin in a 1:2 ratio is more effective orally than a 1:1 ratio. In the case of transdermal delivery, the effectiveness of these complexes is reversed. This shows that the molar ratio of peptide to cyclodextrin is not "routinely determined and optimized by one skill in the art" as the Examiner alleges. Formation of the presently claimed inclusion complexes containing this specific opioid peptide and a cyclodextrin would not have been obvious to a

person of ordinary skill in the art without some teaching in this direction by the cited references. Neither reference cited by the Examiner contains such a teaching. Accordingly, the references cited by the Examiner merely provide an invitation to experiment. These references do not predict that any drug can be combined with cyclodextrins to form orally effective pharmaceutical compositions, nor do they teach how opioid peptides will behave when combined with cyclodextrins.

Accordingly, a person of ordinary skill in the art would have had no motivation to combine these references to arrive at the presently claimed invention without impermissible hindsight. See In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999). The presently claimed complexes were not achieved or suggested by the prior art given that the varying parameters and innumerable possibilities that would have had to be tried until the successful combination was arrived at. Since the prior art does not indicate which parameters are critical, or how the opioid can be expected to behave with cyclodextrin, the only direction as to which of the many choices is likely to be successful is impermissibly provided by the present application. "When a rejection depends on a combination of prior art references there must be some teaching, suggestion, or motivation to combine these references." In re

Rouffet, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). As stated herein, no such motivation is present in the cited references.

Regarding the Examiner's assertion that "Hora et al's description of the cyclodextrins as stabilizing polypeptides in order to maintain their activity...is synonymous with Applicants' desired results of long duration of activity and improved efficacy", this is incorrect. In particular, while the portion of the reference cited by the Examiner does relate to stabilizing polypeptides, it does not disclose that such stabilization is performed in order to maintain the polypeptides activity. In fact, column 19, lines 48-50 implies that most solubilization/stabilization agents provide an "appreciable loss of activity" to the polypeptides which are being stabilized. Accordingly, Hora et al.'s description of the cyclodextrins as stabilizing polypeptides is not actually synonymous with applicant's claimed inclusion complexes having a prolonged activity.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of Hora et al. and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 2, 4, 7-9, 11, and 14.

4. Rejection of claims 1, 7-12, and 15 are rejected over French Patent '268 in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1, 7-12, and 15 are rejected under 35 U.S.C. 103(a) as being obvious over the French Patent '268 in view of the Nath et al article. The French Patent '268 teaches combining drugs, including analgesics and peptide hormones, with B-cyclodextrin. The combination permits the drugs to be administered transcutaneously. See the attached abstract. The French patent '268 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art to at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulation of French Patent '268 because the opioid peptide of the Nath et al article is a specific known example of the analgesic drugs which are contemplated by the French patent '268, because the French patent '268 would have been expected to be useful in transcutaneously administering polypeptides such as the opioid peptide of the Nath et al article because of the French Patent '268's disclosed ability to administer polypeptide hormones, and because administering the opioid peptide of Nath et al transcutaneously in the pharmaceutical formulations of the French Patent '268 would avoid problems of poor absorption after oral administration or of intrusive i.p. administration methods. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and

every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to inclusion complexes comprising an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by Nath et al.

FR '268 does not remedy these deficiencies. FR '268 teaches combining various peptide hormones with a cyclodextrin. This combination permits the drugs to be administered transcutaneously. Indeed, as the Examiner has admitted, FR '268 teaches that transcutaneous administration is used as an alternative to oral administration to "avoid problems of poor absorption after oral administration". Additionally, FR '268 provides no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the drugs used in the disclosed combinations.

In contrast, the presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy which are delivered orally rather than transcutaneously. Applicants appreciate the Examiner's suggestions in this regard and have accordingly amended the claims to emphasize that the present invention is directed to compositions which are orally efficacious, not compositions delivered e.g. transcutaneously.

The Examiner has submitted it is necessary for applicants to submit evidence showing that the compositions disclosed by FR '268 are not orally efficacious. This is unnecessary in the present case, however, as the FR '268 reference on its face demonstrates that the disclosed compositions are not orally efficacious, as admitted by the Examiner.

In particular, as the Examiner has admitted, FR '268 teaches that transcutaneous administration is used as an alternative to oral administration to "avoid problems of poor absorption after oral administration". This reference on its face, then, shows that the disclosed compositions are not orally efficacious; a person of ordinary skill in the art would not expect the disclosed compositions to be effective upon oral administration. In fact, the FR '268 reference specifically relates to compositions delivered transcutaneously because they are not effective when administered orally.

In contrast, the opioid peptides included in the presently claimed inclusion complexes are effective by oral administration, a significant improvement over the teachings of the FR '268 reference. In fact, the data in Tables 2 and 3 of the instant specification, at pages 14 and 15, demonstrate that the presently claimed inclusion complexes are effective via oral administration. A person of ordinary skill in the art would have had no motivation to combine the references cited by the Examiner to arrive at the presently claimed invention as required by In re Fine in view of the fact that FR '268 teaches away from the presently claimed invention requiring a composition which is orally efficacious.

Regarding the Examiner's assertion that "the motivation used to combine the two references is the desirability of forming a transcutaneously administrable composition comprising the compound of the Nath et al article", applicants respectfully reiterate that this combination is not the same as the presently claimed invention. In particular, the presently claimed invention relates to inclusion complexes which are orally efficacious. See claim 1. The combination suggested by the Examiner is transcutaneously administrable, but is not orally efficacious. Accordingly, the Examiner's proposed combination does not result in the same product as that which is presently claimed.

Accordingly, applicants respectfully submit that the presently

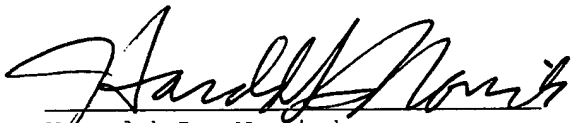
claimed invention is unobvious over Nath et al. in view of FR '268 and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 7-9, 11, and 15.

CONCLUSION

In light of the foregoing, Applicants submit that the application is now in condition for allowance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of all pending claims 1-9, 11, and 14-15 and allow these claims. Favorable action with an early allowance of the claims is earnestly solicited.

Respectfully submitted,

NATH & ASSOCIATES PLLC



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PATENT
Attorney Docket No. 82239

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

DWIVEDI et al.

Examiner: J. RUSSEL

Serial No.: 09/537,088

Art Unit: 1653

Filed: March 29, 2000

For: **NOVEL INCLUSION COMPLEXES OF A HIGH POTENT OPIOID PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF TREATMENT**

Appendix A

Please cancel claims 10 and 12 and amend claim 1 as indicated in the following marked up copy of the claims.

1. (Three Times Amended) An orally efficacious and prolonged duration of action inclusion complex, consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative, wherein said inclusion complex is effective when administered orally to a patient in need thereof.

PATENT
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Filed: March 29, 2000

For: **NOVEL INCLUSION COMPLEXES OF A HIGH POTENT OPIOID PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF TREATMENT**

Appendix B

Please cancel claims 10 and 12 and amend claim 1 as indicated in the following clean copy of the claims.

C1

1. (Three Times Amended) An orally efficacious and prolonged duration of action inclusion complex, consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative, wherein said inclusion complex is effective when administered orally to a patient in need thereof.